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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|-----------------------|---------------------|------------------|
| 09/654,116 | 08/30/2000 | A. Charles Morgan JR. | 180042.418C2 | 6638 |

7590

06/10/2002

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| EXAMINER |
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DUFFY, PATRICIA ANN

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| ART UNIT | PAPER NUMBER |
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1645

DATE MAILED: 06/10/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09 / 654,116

Applicant(s)

Morgan & Inc

Examiner

Duffy

Group Art Unit

1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 2-28-02
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-4-19 is/are pending in the application.
Of the above claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-4-19 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____
 - ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6
- ☒ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other _____

Office Action Summary

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DETAILED ACTION

1. The response filed 2-28-02 has been entered into the record.

Priority

2. The status of nonprovisional parent application(s) (whether patented or abandoned) should be updated. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Specification

3. The title of the invention is not descriptive of the claimed invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

Information Disclosure Statement

4. The information disclosure statement filed 8-21-01 has been considered and an initialed copy is attached.

Election/Restriction

5. Applicant's election of Group I (claims 1-4 and 19) in Paper No. 8 is acknowledged. The election/restriction is moot in view of the cancellation of the non-elected claims.

Claim Rejections - 35 U.S.C. § 101

6. 35 U.S.C. 101 reads as follows:

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Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

7. Claims 1-4 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to growth inhibitory antibodies that antagonize vitamin B12 binding to transcobalamin II (TcII). The claimed invention is drawn to a antibody protein product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 US 566 (1974); American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Inoculant Co. 33 US 127 (1948). Filing of arguments and evidence of a new utility imparted by the increased purity of the claimed invention *and amendment to the claims to recite the essential purity* of the claimed products is suggested to obviate this rejection. For example, "wherein the growth blocking agent is an isolated antibody...".

Claim Rejections - 35 U.S.C. § 112

8. Claims 1-4 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are broadly drawn to any growth blocking agent directed to a vitamin B12 binding site on TcII, the agent being capable of competitively antagonizing or modulating said binding site to inhibit the cellular uptake of vitamin B12. The claims further limit the agent to proteins, peptides, small organic molecules and antibodies.

The specification fails to provide any written description of any growth blocking agent that directed to a vitamin B12 binding site on TcII, the agent being capable of competitively antagonizing or modulating said binding site to inhibit the cellular uptake of vitamin B12. First, there is no written description of the vitamin B12 binding site on TcII. There is no description of any protein, peptide, small organic molecule or antibody with these functional properties. Applicants are claiming all functional equivalents, when the specification fails to disclose even one agent that possesses all the functional requirements of the claim (i.e. growth blocking, directed to a vitamin B12 binding site on TcII, competitively antagonizing or modulating the binding site to inhibit cellular uptake of B12. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has

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not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. The claims encompass a myriad of functional equivalent variants that have no structure in common. The genus of such functional equivalent variants is incalculable and this specification fails to provide clear written description of a single agent that meets the basic function of the claims. As such, the disclosure fails to meet the most basic requirement of written description for the claimed invention.

9. Claims 1-4 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to any growth blocking agent directed to a vitamin B12 binding site on TcII, the agent being capable of competitively antagonizing or modulating said binding site to inhibit the cellular uptake of vitamin B12. The claims further limit the agent to proteins, peptides, small organic molecules and antibodies. The claims encompass of myriad of molecular entities, which in turn encompass of myriad of diverse biochemical properties. The specification fails to teach what residues on TcII are responsible for vitamin B12 binding. Therefore, one skilled in the art would not know what immunogen to use to make antibodies directed to such. Further, one skilled in the art would be unable to predict what potential binding sites would be appropriate to target for the identification of antagonists or modulators. The specification fails to teach even a single beginning molecule or molecules that could be modified to bind and antagonize. Without out guidance as to the structure of such molecules that are directed to the vitamin B12 binding site on TcII, one of skill in the art would have to screen for potential candidates. However, the specification fails to teach what the binding site of vitamin B12 on TcII encompasses and

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as such one would have to resort to screening using apo-TcII. However, it has been well established in the art that screening of agents that bind to receptors, or in this case agents that bind to binding proteins, do not have the ability to determine agonists versus antagonist function, and the art establishes difficulty of excluding "non-specific" inhibition of receptor binding (page 102, first full paragraph, Burch, R.M., Journal of Receptor Research, 11(1-4):101-113, 1991). The state of the art does not allow for accurate design of molecules based solely on function and an undisclosed binding site (vitamin B12 binding site on TcII). Rudinger et al "Peptide Hormones" ed by Parsons et al, University Park Press June 1976, pages 1-7, especially page 6, teaches that "the significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study.". Kuntz et al (Science 257:1078-1082, 1992) discloses that with current technology scientists can not yet design drugs from "first principles" (e.g. page 1078, left column). Though Kuntz et al disclose a particular computational cycle used to combine structural information regarding complementarity between designer drug and target, the method (a) uses X-ray crystallographic or computer generated structural data not set forth in this specification and are known in the art to involve non-routine experimentation and/or results of such are not predictive of *in vivo* activities, (b) of the 100,000 molecules modeled, only 2-20% of 10-50 compounds might show the predicted biological properties, and © the method is characterized by Knutz et al as "problematic" in optimizing leads (e.g. due to difficulties in obtaining proper ligand conformation and discriminating among several proposed interaction modes of similar energy (see e.g. 1059-1061 "Structure-based design"). Further, the same authors question whether the technique will work for compounds other than peptides and oligonucleotides (e.g. page 1061,

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left column "...it is possible to adapt...) and the algorithm is designed for enzyme inhibitors, in contrast to the instant invention. The assays disclosed in the specification do not provide for all the functional information recited in the claims (directed to the vitamin B12 binding site on TcII, growth blocking, antagonizing or modulating the binding site). The courts have held that "... whenever there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement." *Genetech Inc. v. Novo Nordisk A/S* 42USPQ2d 1001.

In the absence of further guidance from Applicants relating to the above noted deficiencies, it would require undue experimentation to make and use the claimed growth blocking agents as claimed.

10. Claims 1-4 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require a growth blocking agent that is directed to a vitamin B12 binding site on TcII. Neither the claims nor the specification teaches the metes and bounds of the vitamin B12 binding site on TcII, as such the metes and bounds of agents "directed to" this site as claimed can not be readily ascertained.

The term "small" in claim 2 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard

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for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The meaning of "antagonizing or modulating said binding site is unclear because in the art the terms "antagonize or modulate" refer to functions, not sequences or sites. An effector function may be antagonized or binding of a natural ligand may be antagonized by addition of an antagonists, however, the binding site itself is not antagonized. Additionally, the specification nor the claims defines the term "modulating" as it relates to binding the vitamin B12 binding site on TcII.

The Markush group of claim 2 is improper, because proteins and peptides are art-recognized macromolecules and thus are dissimilar in core structure to the claimed small organic molecules.

Claim 19 is indefinite because it depends upon canceled claims.

Claim Rejections - 35 U.S.C. § 102 or 103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371[©] of this title before the invention thereof by the applicant for patent. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

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12. In order to be accorded the benefit of the filing date of an earlier application, the earlier application must comply with the requirements under 35 U.S.C. 120. The currently claimed invention either lacks written description (07/880,540; 08/306,540) for the now claimed invention or is not enabled for the claimed invention (08/381,552; 08/476,440). As such, the prior art date for the instantly claimed invention is filing date of the parent application 08/584,949, which is 1/11/96.

13. Claims 1, 2, 3, 4 and 19 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Marcoullis et al, (British Journal of Haematology, 43(1):15-26, 1979).

Marcoullis et al teach the isolation of purification of IgG blocking antibodies for a patient the pernicious anemia. The isolated and purified immunoglobulin neutralized the total unsaturated vitamin B12 binding capacity suggesting that the IgG contained blocking antibodies against transcobalamins. The blocking of the binding of vitamin B12 to transcobalamins resulted in lower serum vitamin B12 levels. The corresponding blocking antibodies are hidden because they prevent the binding of the vitamin to transcobalamins. Because the antibodies block the binding of vitamin B12 to transcobalamins, they necessarily possess the functions recited in the claim (e.g. growth blocking, inhibiting the cellular uptake vitamin B12. Since the Office does not have the facilities for examining and comparing applicant's antibodies with the antibodies of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the antibody of the prior art does not possess the same functional characteristics of the claimed antibody). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

14. Claims 1, 2 and 19 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Shimizu et al, (Oncology, 44(3):169-73, 1987).

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Shimizu et al teach that the compound, methyl-B12, has an antitumor effect *in vitro* and *in vivo* (i.e. as it relates to growth blocking agent). The methyl-B12 was administered in a pharmaceutically acceptable excipient to mice. As such, the derivative and its administration *in vivo* meets the claimed structural and functional limitations of a small organic molecule, absent convincing evidence to the contrary. Since the Office does not have the facilities for examining and comparing applicant's small organic molecules with the growth inhibiting vitamin B12 derivative of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the derivative of the prior art does not possess the same functional characteristics of the claimed small organic molecule). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Citation of Pertinent Prior Art

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Toraya et al (WO 90/10014) discloses new vitamin B12 derivatives, production and applications thereof as neoplasm inhibitors and cell proliferation inhibitors. A translation of this document is not available at this time.

Status of Claims

16. No claims are allowed.

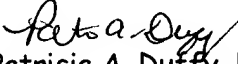
17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the *Official Gazette*, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Thursday and Saturday from 10:30 AM to 7:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
May 30, 2002


Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600